Supplemental Material, Appendix 1. OVID MEDLINE search strategy (1950-March Week 3 2009)

MeSH Term/Key Word	Number of Citations
1. exp Environmental Exposure/	115062
2. exp Environmental Pollutants/	137389
3. exp Pest Control/	16827
4. exp Pesticides/	100239
5. (pesticid$ or herbicid$ or insecticid$ or fungicid$).tw.	48736
6. 1 or 2 or 3 or 4 or 5	318538
7. exp Adolescent/	1276381
8. exp Child/	1268638
9. exp Infant/	778784
10. (child$ or adolescen$ or infant? or newborn? or youth or teenage$).tw.	1044403
11. 7 or 8 or 9 or 10	2533340
12. exp Hematologic Neoplasms/	5919
13. exp Leukemia/	166647
14. leuk?emi$.tw.	168588
15. 12 or 13 or 14	220691
16. 6 and 11 and 15	846

Note: $ = truncation, ? = wildcard

Supplemental Material, Appendix 2. Summary of characteristics and odds ratios for included studies

Reference	Design	Subjects	Exposure index	Exposed cases	Exposure window	Pesticide exposure	Exposure comparison	Odds ratio (95% CI)
1. (Fabia and Thuy 1974), Quebec	Case-control	218 leukemia deaths[a], 772 controls, age <5 yr	Occupation in farming on birth records	16 case fathers	Before child's birth	Unspecified pesticides	Yes/no	Paternal 0.70 (0.39-1.21)[b]
2. (van Steensel-Moll et al. 1985), The Netherlands	Case-control	625 ALL cases, 615 controls, age <15	Self-reported occupational pesticide exposure in agriculture, horticulture, or forestry	36 case fathers, 4 case mothers	Pregnancy	Unspecified pesticides	Yes/no	Maternal 0.7 (0.2-2.5) Paternal 1.0 (0.6-1.7)
3. (Lowengart et al. 1987), Los Angeles County	Case-control	123 leukemia cases, 123 matched controls, age 0-10	Self-reported occupation in farming	6 case fathers	1 yr before conception to 1 yr before diagnosis	Unspecified pesticides	Yes/no	Paternal 1.0 (0.27-3.74)
4. (Shu et al. 1988), Shanghai	Case-control	204 leukemia cases, 204 matched controls, age <15	Self-reported occupation in agriculture	2 case fathers	Pregnancy	Unspecified pesticides	Yes/no	Paternal 0.3 (0.1-1.6)
			Self-reported occupational pesticide exposure in agriculture	12 case mothers	Pregnancy	Unspecified pesticides	Yes/no	Maternal Total leukemia 2.6 (0.8-9.1) ALL 3.5 (1.1-11.2) AML 2.4 (0.5-11.0)
5. (Laval and Tuyns 1988), France	Case-control	201 leukemia cases, 201 matched controls	Self-reported occupational pesticide exposure; no details on job titles or industry linked to exposure	12 case fathers[c]	Exposure timing not specified	Unspecified pesticides	Yes/no	Paternal 4.97 (1.46-22.2)[d]

[a] May have included a few lymphoma deaths
[b] Crude odds ratio, calculated from data in paper
[c] No breakdown of maternal vs paternal exposure; assumed to be mainly paternal
[d] Crude OR calculated from data in paper

Reference	Design	Subjects	Exposure index	Exposed cases	Exposure window	Pesticide exposure	Exposure comparison	Odds ratio (95% CI)
6. (Buckley et al. 1989), Children's Cancer Group, USA, Canada	Case-control	204 cases acute myeloid leukemia (AML), matched controls, age <18	Self-reported occupational pesticide exposure	27 case fathers	1 yr before birth to diagnosis	Unspecified pesticides	Cumulative exposure frequency, >1000 vs 0 d	Paternal 2.7 (1.0-7.0) p-trend=.06
			Self-reported occupational pesticide exposure	11 case mothers	1 yr before birth to diagnosis	Unspecified pesticides	Cumulative exposure frequency, ≥1 vs 0 d	Maternal 2.85 (0.82-10.8)[3]
7. (Danila 1989), Minnesota, Wisconsin, North Dakota, Michigan	Case-control	151 ALL cases, 149 controls, age <16 yr	Self-reported agricultural pesticide exposure	4 case mothers	Pregnancy	Direct exposure, farm pesticides	Yes/no	Maternal Livestock insecticides 3.20 (0.26-170.4)
			Self-reported agricultural pesticide exposure	39, 18, 25, 5 and 2 case fathers, respectively, exposed to livestock insecticides, crop insecticides, herbicides, fungicides or fumigants	Any preconceptual exposure	Direct exposure, farm pesticides	Yes/no	Paternal Livestock insecticides 1.90 (0.69-5.26) Herbicides 1.10 (0.45-2.72) Fungicides 0.98 (0.24-4.02) Fumigants 0.68 (0.11-5.30)
8. (Gardner et al. 1990), UK	Case-control	52 cases leukemia, 277 controls, age <25 yr	Paternal occupation in farming on birth records	5 case fathers	Before child's birth	Unspecified pesticides	Yes/no, local controls	Paternal 2.63 (0.77-8.95)
9. (Magnani et al. 1990), Turin, Italy	Case-control	142 ALL, 22 AML cases, 307 controls	Self-reported occupation in farming	4 case fathers	Before child's birth	Unspecified pesticides	Yes/no	Paternal 1.8 (0.5-6.5)
10. (Infante-Rivard et	Case-control	128 ALL cases, 128 controls, age	Self-reported occupational	7 case mothers	Pregnancy	Insecticides	Yes/no	Maternal

Reference	Design	Subjects	Exposure index	Exposed cases	Exposure window	Pesticide exposure	Exposure comparison	Odds ratio (95% CI)
al. 1991), Spain		<15	insecticide exposure in agriculture					1.40 (0.44-4.41)
11. (Kishi et al. 1993), Japan	Case-control	103 ALL cases, 264 controls[e]	Self-reported occupation in farming	9 case mothers	Pregnancy	Unspecified pesticides	Yes/no, pop controls	Maternal 4.0 (1.1-14.0)
			Self-reported occupational pesticide exposure	Not stated	Pregnancy[f]	Unspecified pesticides	Yes/no, pop controls	Paternal 2.07 (0.90-5.06)
12. (Roman et al. 1993), UK	Case-control	50 leukemia and 4 NHL cases, 324 controls, age 0-4	Paternal occupation in farming on birth records[g]	2 case fathers	Before child's birth	Unspecified pesticides	Yes/no	Paternal 1.1 (0.1-5.9)
13. (Steinbuch 1994), Ohio	Case-control	271 AML cases, 322 controls, age <18 yr	Self-reported occupational pesticide exposure	19 case mothers	Pregnancy	Unspecified pesticides	Yes/no	Maternal 1.74 (0.83-3.65)
				16 case mothers		Insecticides[h]	Yes/no	1.65 (0.76-3.68)
				3 case mothers		Herbicides	Yes/no	1.97 (0.34-13.9)
14. (Meinert et al. 1996), Germany	Case-control	173 leukemia cases, 220 local controls[i], age <15 yr	Self-reported occupational pesticide exposure, mainly in agriculture	2 case mothers	Pregnancy	Unspecified pesticides	Yes/no	Maternal 2.68 (0.20-79.4)[j]
				9 case fathers	Year before conception	Unspecified pesticides	Yes/no	Paternal 1.29 (0.48-3.41)[k]

[e] Used data for population controls only (paper also gave data for hospital controls)
[f] Data for preconceptual exposure not available
[g] Paper also gave data for occupation at child's diagnosis
[h] Includes unknown pesticides used to kill cockroaches, ants or other insects
[i] Paper also included data for state controls
[j] Crude OR, calculated from data in paper by assuming 1 instead of 0 exposed control mothers
[k] Crude OR, calculated from data in paper

Reference	Design	Subjects	Exposure index	Exposed cases	Exposure window	Pesticide exposure	Exposure comparison	Odds ratio (95% CI)
15. (Kristensen et al. 1996), Norway	Retrospective cohort	149,254 farm holders (84% males), 323,292 offspring born during 1952-91, 181 leukemia cases age <40 yr during 1965-1991	Farm holders identified from agriculture censuses; 27% reported pesticide purchases	52 cases on farms with pesticide purchases	Ambiguous[l]	Unspecified pesticides	Yes/no	Paternal Total leukemia 1.06 (0.75-1.49) ALL 1.03 (0.65-1.64) AML 1.35 (0.64-2.85)
16. (Infante-Rivard and Sinnett 1999), Montreal	Case-control	491 ALL cases, 491 controls, age <10 yr	Self-reported occupational pesticide exposure	66, 50, 19 and 15 case fathers, respectively, exposed to any pesticide, insecticides, herbicides or fungicides	Any preconceptual	Broad pesticide classes	Yes/no	Paternal Any pesticide 1.56 (1.02-2.40) Insecticides 1.38 (0.87-2.18) Herbicides 2.05 (0.93-4.56) Fungicides 5.11 (1.46-17.8)
17. (Heacock et al. 2000), British Columbia	Nested case-control	Cohort of 23,829 sawmill workers and their offspring; 40 cases, 200 controls, age <20 yr	Job title and work history used to compute cumulative chlorophenate exposure hours	5 case fathers exposed 3560+ hr	Cumulative preconceptual	Chlorophenate wood preservatives	≥3560 vs <3000 hours cumulative exposure	Paternal 0.8 (0.2-3.6)
18. (Meinert et al. 2000), Germany	Case-control	1184 leukemia cases, 2588 controls, age <15 yr	Self-reported occupational pesticide exposure, mainly in agriculture	15 case mothers	Pregnancy	Unspecified pesticides	Yes/no	Maternal 3.6 (1.5-8.8)
			Self-reported occupational pesticide exposure, mainly in	62 case fathers	Year before conception	Unspecified pesticides	Yes/no	Paternal 1.5 (1.1-2.2)

[l] Preconceptual or prenatal exposure only likely for younger cases

Reference	Design	Subjects	Exposure index	Exposed cases	Exposure window	Pesticide exposure	Exposure comparison	Odds ratio (95% CI)
			agriculture					
19. (Wen et al. 2000), USA, Canada	Case-control	2746 (1805 ALL, 528 AML, other) cases, 3157 (2051 matched to ALL, 657 matched to AML) controls, age <18 yr	Self-reported history of herbicide exposure during military service in Vietnam	28 case fathers	Up to 15+ yrs before conception	Agent Orange (50:50 mix of 2,4-D and 2,4,5-T)	Yes/no	Paternal Total leukemia 1.1 (0.6-1.8) ALL 1.2 (0.6-2.2) AML 0.9 (0.3-2.9)
				21 case fathers		Other herbicides	Yes/no	Paternal Total leukemia 1.8 (0.9-3.5) ALL 1.8 (0.8-4.0) AML 1.8 (0.5-6.3)
20. (Feychting et al. 2001), Sweden	Retrospective cohort.	161 leukemia cases among 235,635 children of married couples born soon after 2 censuses, age <15 yr	Census record occupation in agriculture, horticulture, or forestry	5 case fathers	2-26 mos before child's birth	Unspecified pesticides	Possible or likely exposure, yes/no	Paternal 0.90 (0.37-2.19)
21. (Alexander et al. 2001), international study	Case-control	136 leukemia cases, 266 controls, age<18 months	Self-reported occupational pesticide exposure	15 case mothers	Pregnancy	Unspecified pesticides	Yes/no	Maternal Total leukemia 3.67 (1.54-8.74) ALL 2.53 (0.71-8.97) AML 5.08 (1.84-14.0)
				7 case mothers	Pregnancy	Insecticides	Yes/no	Maternal Total

Reference	Design	Subjects	Exposure index	Exposed cases	Exposure window	Pesticide exposure	Exposure comparison	Odds ratio (95% CI)
								leukemia 5.14 (1.27-20.9) ALL 4.30 (0.66-28.1) AML 7.82 (1.73-35.4)
22. (Rodvall et al. 2003), Sweden	Retrospective cohort	8 leukemia cases among 27,329 offspring of 20,245 male pesticide applicators, mean age 9.3 yr (range not stated)	Licensed pesticide applicators	8 case fathers	Up to 29 yr before child's birth	Unspecified pesticides	Yes/no	Paternal 0.43 (0.19-0.86)
23. (McKinney et al. 2003), UK Childhood Cancer Study	Case-control	1737 leukemia cases, 7600 controls, age<15 yr	Self-reported use of agrochemicals	5 case mothers	1 year before birth	Unspecified pesticides	Yes/no	Maternal 0.81 (0.31-2.12)
				36 case fathers	1 year before birth	Unspecified pesticides	Yes/no	Paternal 0.83 (0.58-1.19)
24. (Flower et al. 2004), Agriculture Health Study, Iowa, USA	Prospective cohort	9 leukemia cases among 17537 children of licensed agriculture pesticide applicators, age <20 yr	Licensed agriculture pesticide applicators (99% male)	9 case fathers	Any preconceptual	Unspecified pesticides	Yes/no	Paternal 0.91 (0.47-1.75)
25. (Dell 2004), Pittsburgh	Case-control	49 cases leukemia, 97 controls, age <18 yr	Self-reported occupational pesticide exposure	2 case fathers	2 years before conception	Unspecified pesticides	Yes/no	Paternal 1.00 (0.16-6.14)
26. (Abadi-Korek et al. 2006), Israel	Case-control	112 childhood ALL cases, 112 controls, age not stated	Self-reported job in farming with likely pesticide exposure for at least 6 mos	45 case parents	Before diagnosis	Unspecified pesticides	Yes/no	Paternal 2.35 (1.10-5.0)

Reference	Design	Subjects	Exposure index	Exposed cases	Exposure window	Pesticide exposure	Exposure comparison	Odds ratio (95% CI)
27. (Menegaux et al. 2006), France	Case-control	280 leukemia cases, 288 controls, age<15 yr	Self-reported occupational pesticide exposure	2 case mothers	Pregnancy	Unspecified pesticides	Yes/no	Maternal 2.06 (0.16-61.1)[m]
28. (Pearce et al. 2006),	Case-control	4727 leukemia cases, 428,842 controls[n], age<25 yr	Paternal occupation in farming, forestry, horticulture or gardening on birth records	34, 23 and 7 fathers, respectively, of any leukemia, ALL and AML cases	Before child's birth	Unspecified pesticides	Yes/no	Paternal Total leukemia 0.38 (0.27-0.55) ALL 0.37 (0.24-0.57) AML 0.36 (0.17-0.77)
29. (Rudant et al. 2007), France	Case-control	764 leukemia cases, 1682 controls, age<15 yr	Self-reported occupational pesticide exposure	21 case mothers	Pregnancy	Unspecified pesticides	Yes/no	Maternal 1.2 (0.7-2.0)
			Self-reported occupation in agriculture	20 case fathers	Pregnancy	Unspecified pesticides	Yes/no	Paternal 0.6 (0.4-1.1)
30. (Monge et al. 2007), Costa Rica	Case-control	300 leukemia cases, 579 controls, age<15 yr	Self-reported occupational pesticide exposure in agriculture	11, 7, 8 and 4 case mothers, respectively, exposed to any pesticide, insecticides, herbicides or fungicides	Pregnancy	Broad classes	Yes/no	Maternal Any pesticide 4.5 (1.4-14.7) Insecticides 6.9 (1.4-33.2) Herbicides 5.3 (1.4-20) Fungicides 7.8 (0.9-71)
				64, 41, 53 and 30 case fathers, respectively, exposed to any pesticide, insecticides, herbicides or fungicides	Year before conception	Broad classes	Yes/no	Paternal Any pesticide 1.2 (0.9-1.8) Insecticides

[m] Crude OR, calculated from data in paper
[n] Live births matched for sex and YOB

Reference	Design	Subjects	Exposure index	Exposed cases	Exposure window	Pesticide exposure	Exposure comparison	Odds ratio (95% CI)
								1.4 (0.9-2.1) Herbicides 1.2 (0.8-1.7) Fungicides 1.6 (1.0-2.6)
31. (Perez-Saldivar et al. 2008), Mexico City	Case-control	193 acute leukemia cases, 193 matched hospital controls	Self-reported paternal occupation in farming for at least 6 months	7 case fathers	2 yr before conception	Unspecified pesticides	Yes/no	Paternal 2.91 (0.44-19.2)

Supplemental Material, Appendix 3. Modified Downs and Black study quality assessment tool

Case-control Studies

Factor	Score
External Validity 1. *Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* Cases and controls were representative of the source population of interest (population- or cohort-based cases and controls), the source population was identified, and subject selection described.	1
2. *Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* Participation rate for cases and controls of at least 70%.	1
Subtotal	2
Internal Validity – Bias 3. *Was an attempt made to blind those measuring the main outcomes of the intervention?* Exposure ascertainment was based on interviews blinded to health outcome status, mailed questionnaire, or other pre-existing or documented exposure information.	1
4. *If any of the results of the study were based on "data dredging", was this made clear?* The study was designed to examine the reported association.	1
5. *In case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Cases and controls were age matched and the exposure period examined was well-defined.	1
6. *Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used were appropriate for the study design and sample size.	1
7. *Was compliance with the intervention reliable?* The effect of exposure misclassification was likely to bias the reported association towards the null. For example, exposure status based on pre-existing or documented information exposure information (not retrospective case interviews).	1
8. *Were the main outcome measures used accurate (valid and reliable)?* Outcome measurement was clearly described and was virtually certain (histologically confirmed cancer cases).	1
Subtotal	6
Internal Validity – Exposure Measurement 9[a]. *Were measures of exposure robust?* Exposure status was either documented or determined via biomarker (2); used small area ecological measures, job titles, or was self-reported (1); was based on large area ecological measures (0).	2
10[a]. *Was there a sufficient exposure gradient?* The degree of variability between categories of exposure frequency, duration, or intensity was high (2), medium (1), low/unknown (0).	2
11[a]. *Were measures of exposure specific?* Exposure measures were specific (2); based on broader, chemically-related groups (1); based on broad groupings of diverse chemical and toxicological properties (0).	2
12[a]. *Were all critical exposure time windows measured and reported?* Exposure time windows were all (2); partially (1); or not at all defined, measured, and reported (0).	2
Subtotal	8
Internal Validity – Confounding 13. *Were the cases and controls recruited from the same population?* Information on the source of study participants provided; controls representative of the study base from which cases are drawn.	1
14. *Were the cases and controls recruited over the same period of time?* The calendar period over which cases and controls were recruited was defined and similar.	1
15. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* The study collected data on all major (2), some (including basic demographic only) (1), or no (0) potential confounders and assessed their effect in analysis.	2
Subtotal	4
Total	20

[a] item added to the checklist by authors

Note: here 'intervention' equates to 'exposure' in an observational study

Cohort Studies

Factor	Score
External Validity 1. *Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* Subjects were representative of the source population of interest, the source population was identified, subject selection described, and subjects disease-free at baseline.	1
2. *Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* Participation rate for subjects at least 70% or distribution of key sociodemographic and confounding variables representative of source population.	1
Subtotal	2
Internal Validity – Bias 3. *Was an attempt made to blind those measuring the main outcomes of the intervention?* Ascertainment of health outcomes equal for exposed and unexposed subjects.	1
4. *If any of the results of the study were based on "data dredging", was this made clear?* The study was designed to examine the reported association.	1
5. *In cohort studies, do the analyses adjust for different lengths of follow-up of subjects?* Follow-up time period was the same for all study subjects or adjusted for in analysis.	1
6. *Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used were appropriate for the study design and sample size.	1
7. *Was compliance with the interventions reliable?* Ascertained any change during followup of exposure status at baseline	1
8. *Were the main outcome measures used accurate (valid and reliable)?* Outcome measurement was clearly described and was virtually certain (histologically confirmed cancer cases).	1
Subtotal	6
Internal Validity – Exposure Measurement 9[a]. *Were measures of exposure robust?* Exposure status was either documented or determined via biomarker (2); used small area ecological measures, job titles, or was self-reported (1); was based on large area ecological measures (0).	2
10[a]. *Was there a sufficient exposure gradient?* The degree of variability between categories of exposure frequency, duration, or intensity was high (2), medium (1), low/unknown (0).	2
11[a]. *Were measures of exposure specific?* Exposure measures were specific (2); based on broader, chemically-related groups (1); based on broad groupings of diverse chemical and toxicological properties (0).	2
12[a]. *Were all critical exposure time windows measured and reported?* Exposure time windows were all (2); partially (1); or not at all defined, measured, and reported (0).	2
Subtotal	8
Internal Validity – Confounding 13. *Were study subjects in different exposure groups recruited from the same population?* Information on the source of study participants provided and similar.	1
14. *Were study subjects in different exposure groups recruited over the same period of time?* The calendar period over which subjects were recruited and followed up was defined and similar.	1
15. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* The study collected data on all major (2), some (including basic demographic only) (1), or no (0) potential confounders and assessed their effect in analysis.	2
Subtotal	4
Total	20

[a] item added to the checklist by authors

Note: here 'interventions' equates to 'exposure' in an observational study

Supplemental Material, Appendix 4. Pesticide exposure by parent, time window, and exposure index

Pesticide exposure indices	References
Paternal	
Well-defined preconceptual window	
a) Preconceptual period <2 years	
Occupational pesticide exposure during year before conception	(Meinert et al. 1996)
Occupational pesticide exposure during year before conception	(Meinert et al. 2000)
Occupational pesticide exposure during 2 yr before conception	(Dell 2004)
Occupational pesticide exposure during 1 yr before conception	(Monge et al. 2007)
Occupation in farming for 6+ months during 2 yr before conception	(Perez-Saldivar et al. 2008)
b) Preconceptual exposure reasonably inferable[a]	
Occupation in farming at child's birth	(Fabia and Thuy 1974)
Occupational pesticide exposure during pregnancy	(van Steensel-Moll et al. 1985)
Occupation in farming during pregnancy	(Shu et al. 1988)
Occupation in farming at child's birth	(Gardner et al. 1990)
Occupational pesticide exposure during pregnancy	(Kishi et al. 1993)
Occupation in farming at child's birth	(Roman et al. 1993)
Job title with likely pesticide exposure 2-26 mos before child's birth	(Feychting et al. 2001)
Agricultural chemical use during 1 yr before child's birth	(McKinney et al. 2003)
Job title with likely pesticide exposure at child's birth	(Pearce et al. 2006)
Occupation in farming during pregnancy	(Rudant et al. 2007)
Ill-defined exposure window	
Occupation in farming 1 yr before conception to 1 yr before diagnosis	(Lowengart et al. 1987)
Any occupational pesticide exposure 1 yr before birth to diagnosis	(Buckley et al. 1989)
Any preconceptual agricultural pesticide use	(Danila 1989)
Occupation in farming before child's birth	(Magnani et al. 1990)
Occupational pesticide exposure during preconceptual period[b]	(Infante-Rivard and Sinnett 1999)
Farmer licensed as pesticide applicator during preconceptual period	(Flower et al. 2004)
Parental occupational pesticide exposure[c]; timing not stated	(Laval and Tuyns 1988)
Occupation as farmer and record of pesticide purchases[d]	(Kristensen et al. 1996)
Cumulative lifetime occupational chlorophenate exposure[e]	(Heacock et al. 2000)
Occupational herbicide exposure up to 15+ yrs before conception	(Wen et al. 2000)
Licensed as pesticide applicator up to 29 yr before child's birth	(Rodvall et al. 2003)
Job title with likely pesticide exposure before date of diagnosis[f]	(Abadi-Korek et al. 2006)
Maternal	
Well-defined pregnancy window	
a) During pregnancy	
Occupational pesticide exposure during pregnancy	(van Steensel-Moll et al. 1985)
Occupation in farming during pregnancy	(Shu et al. 1988)
Agricultural pesticide use during pregnancy	(Danila 1989)
Occupational pesticide use during pregnancy	(Infante-Rivard et al. 1991)
Occupation in farming during pregnancy	(Kishi et al. 1993)
Occupational pesticide exposure during pregnancy	(Steinbuch 1994)
Occupational pesticide exposure during pregnancy	(Meinert et al. 1996)
Occupational pesticide exposure during pregnancy	(Meinert et al. 2000)
Occupational pesticide exposure during pregnancy	(Alexander et al. 2001)
Occupational pesticide exposure during pregnancy	(Menegaux et al. 2006)

Occupational pesticide exposure during pregnancy	(Rudant et al. 2007)
Occupational pesticide exposure during 1st or 2nd trimester	(Monge et al. 2007)
b) Pregnancy exposure reasonably inferable	
Agricultural chemical use during 1 yr before child's birth	(McKinney et al. 2003)
Ill-defined exposure window	
Any occupational pesticide exposure 1 yr before birth to diagnosis	(Buckley et al. 1989)

[a] Some studies of paternal pesticide exposure only assessed exposure during pregnancy or paternal occupation at birth; we deemed these to be reasonable proxies for preconceptual exposure, assuming that paternal occupations likely did not change from preconception to pregnancy (23 of the 27 paternal occupations were in farming).
[b] Duration not stated
[c] Assumed to be mainly paternal
[d] Timing ambiguous; preconceptual exposure likely only for younger cases
[e] At least 3560 hours cumulative exposure from initial employment until diagnosis
[f] Data presented only for exposure of either parent

Appendix 5. Study quality factor scores[a]

Study number[b]	Reference	Year	Design	External validity	Internal validity: bias	Internal validity: exposure measurement	Internal validity confounding	Total score
17	(Heacock et al. 2000), British Columbia	2000	Cohort[c]	2	6	6	3	17
30	(Monge et al. 2007), Costa Rica	2007	C-C[d]	2	5	5	3	15
19	(Wen et al. 2000), USA, Canada	2000	C-C	2	4	4	4	14
6	(Buckley et al. 1989), USA, Canada	1989	C-C	2	4	4	3	13
13	(Steinbuch 1994), Ohio	1994	C-C	2	4	4	3	13
1	(Fabia and Thuy 1974), Quebec	1974	C-C	2	6	2	2	12
8	(Gardner et al. 1990), UK	1990	C-C	2	6	2	2	12
15	(Kristensen et al. 1996), Norway	1996	Cohort	2	6	1	3	12
16	(Infante-Rivard and Sinnett 1999), Montreal	1999	C-C	2	4	3	3	12
20	(Feychting et al. 2001), Sweden	2001	Cohort	2	6	2	2	12
22	(Rodvall et al. 2003), Sweden	2003	Cohort	2	6	2	2	12
24	(Flower et al. 2004), Iowa, USA	2004	Cohort	2	6	1	3	12
28	(Pearce et al. 2006), England	2006	C-C	1	6	2	3	12
29	(Rudant et al. 2007), France	2007	C-C	2	4	3	3	12
7	(Danila 1989), Minnesota, Wisconsin, North Dakota, Michigan	1989	C-C	1	3	4	3	11

Study number[b]	Reference	Year	Design	External validity	Internal validity: bias	Internal validity: exposure measurement	Internal validity confounding	Total score
12	(Roman et al. 1993), UK	1993	C-C	2	5	1	3	11
18	(Meinert et al. 2000), Germany	2000	C-C	2	4	3	2	11
4	(Shu et al. 1988), Shanghai	1988	C-C	2	4	2	3	11
2	(van Steensel-Moll et al. 1985), The Netherlands	1985	C-C	1	5	2	2	10
10	(Infante-Rivard et al. 1991), Spain	1991	C-C	2	5	1	2	10
21	(Alexander et al. 2001), international study	2001	C-C	0	4	3	3	10
11	(Kishi et al. 1993), Japan	1993	C-C	1	3	3	2	9
14	(Meinert et al. 1996), Germany	1996	C-C	2	3	2	2	9
23	(McKinney et al. 2003), UK Childhood Cancer Study	2003	C-C	1	4	2	2	9
25	(Dell 2004), Pittsburgh	2004	C-C	1	4	3	1	9
3	(Lowengart et al. 1987), Los Angeles County	1987	C-C	1	4	2	2	9
27	(Menegaux et al. 2006), France	2006	C-C	1	3	2	2	8
31	(Perez-Saldivar et al. 2008), Mexico City	2008	C-C	1	5	2	1	8
26	(Abadi-Korek et al. 2006), Israel	2006	C-C	0	3	1	3	7
9	(Magnani et al. 1990), Turin, Italy	1990	C-C	0	3	2	0	5

Study number[b]	Reference	Year	Design	External validity	Internal validity: bias	Internal validity: exposure measurement	Internal validity confounding	Total score
5	(Laval and Tuyns 1988), Lyon, France	1988	C-C	0	2	1	2	5

C-C = case-control

REFERENCES

Abadi-Korek I, Stark B, Zaizov R, Shaham J. 2006. Parental occupational exposure and the risk of acute lymphoblastic leukemia in offspring in Israel. J Occup Environ Med 48:165-174.

Alexander FE, Patheal SL, Biondi A, Brandalise S, Cabrera ME, Chan LC et al. 2001. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. Cancer Res 61:2542-2546.

Buckley JD, Robison LL, Swotinsky R, Garabrant DH, LeBeau M, Manchester P et al. 1989. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Childrens Cancer Study Group. Cancer Res 49:4030-4037.

Danila RN. 1989. An epidemiologic study of acute lymphocytic leukemia in children less than sixteen years - an evaluation of potential risk factors with emphasis on farm exposures. Minnesota, USA: University of Minnesota.

Dell DM. 2004. Epidemiology of childhood leukemia: Environmental and genetic determinants. ProQuest Information and Learning Company, Ann Arbor, Michigan: University of Pittsburgh, Pittsburgh, Pennsylvania.

Fabia J, Thuy TD. 1974. Occupation of father at time of birth of children dying of malignant diseases. Br J Prev Soc Med 28:98-100.

Feychting M, Plato N, Nise G, Ahlbom A. 2001. Paternal occupational exposures and childhood cancer. Environ Health Perspect 109:193-196.

Flower KB, Hoppin JA, Lynch CF, Blair A, Knott C, Shore DL et al. 2004. Cancer risk and parental pesticide application in children of agricultural health study participants. Environ Health Perspect 112:631-635.

Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. 1990. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. Brit Med J 300:423-429.

Heacock H, Hertzman C, Demers PA, Gallagher R, Hogg RS, Teschke K et al. 2000. Childhood cancer in the offspring of male sawmill workers occupationally exposed to chlorophenate fungicides. Environ Health Perspect 108:499-503.

Infante-Rivard C, Mur P, Armstrong B, Alvarez-Dardet C, Bolumar F. 1991. Acute lymphoblastic leukaemia among Spanish children and mothers' occupation: a case-control study. J Epidemiol Community Health 45:11-15.

Infante-Rivard C, Sinnett D. 1999. Preconceptional paternal exposure to pesticides and increased risk of childhood leukaemia . Lancet 354:1819.

Kishi R, Katakura Y, Yuasa J, Miyake H. 1993. Association of parents' occupational exposure to cancer in children (Japanese). Jpn J Ind Health 35:515-529.

Kristensen P, Andersen A, Irgens LM, Bye AS, Sundheim L. 1996. Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. Int J Cancer 65:39-50.

Laval G, Tuyns AJ. 1988. Environmental factors in childhood leukaemia. Br J Ind Med 45:843-844.

Lowengart RA, Peters JM, Cicioni C, Buckley J, Bernstein L, Preston-Martin S et al. 1987. Childhood leukemia and parents' occupational and home exposures. J Natl Cancer Inst 79:39-46.

Magnani C, Pastore G, Luzzatto L, Terracini B. 1990. Parental occupation and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: a case-control study. Tumori 76:413-419.

McKinney PA, Fear NT, Stockton D. 2003. Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study. Occup Environ Med 60:901-909.

Meinert R, Kaatsch P, Kaletsch U, Krummenauer F, Miesner A, Michaelis J. 1996. Childhood leukaemia and exposure to pesticides: results of a case-control study in northern Germany. Eur J Cancer 32A:1943-1948.

Meinert R, Schuz J, Kaletsch U, Kaatsch P, Michaelis J. 2000. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. Am J Epidemiol 151:639-646.

Menegaux F, Baruchel A, Bertrand Y, Lescoeur B, Leverger G, Nelken B et al. 2006. Household exposure to pesticides and risk of childhood acute leukaemia. Occup Environ Med 63:131-134.

Monge P, Wesseling C, Guardado J, Lundberg I, Ahlbom A, Cantor KP et al. 2007. Parental occupational exposure to pesticides and the risk of childhood leukemia in Costa Rica. Scand J Work Environ Health 33:293-303.

Pearce MS, Hammal DM, Dorak MT, McNally RJ, Parker L. 2006. Paternal occupational exposure to pesticides or herbicides as risk factors for cancer in children and young adults: a case-control study from the North of England. Arch Environ Occup Health 61:138-144.

Perez-Saldivar ML, Ortega-Alvarez MC, Fajardo-Gutierrez A, Bernaldez-Rios R, Del Campo-Martinez Mde L, Medina-Sanson A et al. 2008. Father's occupational exposure to carcinogenic agents and childhood acute leukemia: a new method to assess exposure (a case-control study). BMC Cancer 8:7 (e-pub).

Rodvall Y, Dich J, Wiklund K. 2003. Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. Occup Environ Med 60:798-801.

Roman E, Watson A, Beral V, Buckle S, Bull D, Baker K et al. 1993. Case-control study of leukaemia and non-Hodgkin's lymphoma among children aged 0-4 years living in west Berkshire and north Hampshire health districts. Brit Med J 306:615-621.

Rudant J, Menegaux F, Leverger G, Baruchel A, Nelken B, Bertrand Y et al. 2007. Household exposure to pesticides and risk of childhood hematopoietic malignancies: The ESCALE study (SFCE). Environ Health Perspect 115:1787-1793.

Shu XO, Gao YT, Brinton LA, Linet MS, Tu JT, Zheng W et al. 1988. A population-based case-control study of childhood leukemia in Shanghai. Cancer 62:635-644.

Steinbuch M. 1994. The role of environmental exposures in the etiology of childhood acute myeloid leukemia. Ohio, USA: Ohio State University.

van Steensel-Moll HA, Valkenburg HA, van Zanen GE. 1985. Childhood leukemia and parental occupation. A register-based case- control study. Am J Epidemiol 121:216-224.

Wen WQ, Shu XO, Steinbuch M, Severson RK, Reaman GH, Buckley JD et al. 2000. Paternal military service and risk for childhood leukemia in offspring. Am J Epidemiol 151:231-240.